DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

3047 '00 APR 24 A10 :31

APR 18 2000

Mitchall G. Clark
4365 McConnell Ave
Los Angeles, CA 90066

Docket No. 00P-0091/CP1

Dear Mr. Clark:

This is in response to your petition filed on January 4, 2000. We also refer to your petition 99P-1653/CP1 that was filed on May 25, 1999, and withdrawn on October 14, 1999 and to our letter requesting additional information dated October 22, 1999. You are requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug products: Pamidronate Disodium Injection, 3 mg/mL, 10 mL vials (total drug content 30 mg), and 9 mg/mL, 10 mL vials (total drug content 90 mg). The listed drug products to which you refer in your petition are Aredia® (Pamidronate Disodium for Injection) 30mg/vial and 90 mg/vial manufactured by Novartis.

Your request involves a change in dosage form from that of the listed drug product (i.e., from a (dry solid) for injection to a (ready-to-use) injection). The change you request is the type of change that is authorized under the Act.

We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act) and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced drug products.

This petition was evaluated with respect to the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule, published in the Federal Register (Pediatric Rule)(63 FR 66632) and with respect to the requirements of Section 505(j)(2)(C) of the Act. The Agency has determined that your proposed change in dosage form is subject to the Pediatric Rule but that a full waiver of the pediatric study requirement under 21 C.F.R. § 314.55(c)(2)(ii) is appropriate. The Agency has concluded that investigations are not necessary to demonstrate the safety and effectiveness of your proposed products in the pediatric population since the necessary studies are impossible or highly impractical because the number of such patients is small and geographically dispersed. In addition, the Agency has determined that investigations are not necessary to show safety and efficacy in the adult population.

Under the Pediatric Rule, "each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration" must contain "data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric

00P-0091

PAV1

subpopulation for which the drug is safe and effective." 21 C.F.R. § 314.55(a). The Agency may waive the study requirements for some or all pediatric age groups if it concludes that:

(1) (a) The product does not represent a meaningful therapeutic benefit[1] over existing treatments, and (b) the product was not likely to be used in a substantial number of pediatric patients (21 C.F.R. § 314.55(c)(2)(i)); or

(2) the necessary studies are impossible or highly impractical, because, for example, the number of such patients is so small or geographically dispersed (21 C.F.R. § 314.55(c)(2)(ii)); or

(3) there is evidence strongly suggesting that the product would be ineffective or unsafe in some or all pediatric populations (21 C.F.R. § 314.55(c)(2)(iii)).

The waiver request submitted in your petition dated December 29, 1999, argued that:

(1) The change in dosage form from pamidronate disodium lyophilized powder to a ready to use aqueous form of pamidronate disodium is a pharmaceutical change only, not a change in dosage form and therefore does not trigger the Pediatric Rule under 21 C.F.R. § 314.55(a). You contended that the proposed product is identical to the reference product (Aredia) when Aredia is reconstituted as described in the labeling.

(2) The proposed change does not represent a meaningful therapeutic benefit over the reference product or other existing treatments.

(3) Pamidronate disodium is indicated for use in patients with Paget's Disease, hypercalcemia of malignancy, osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. All of these diseases are primarily diseases of the adult population. Therefore pamidronate disodium will not be used in a substantial number (>50,000) of pediatric patients.

The Agency's response to your waiver request follows:

(1) The Agency considers a [Drug] for injection, and a [Drug] injection as different dosage forms; and these dosage forms are listed in separate monographs (e.g., Doxorubicin Hydrochloride Injection and Doxorubicin Hydrochloride for Injection) in the United States Pharmacopoeia (USP) (Please refer to General Chapter <1> in the USP). Because you are requesting a change to a new dosage form, you are subject to the Pediatric Rule under 21 C.F.R. § 314.55(a).

(2) You do not qualify for waiver under 21 C.F.R. § 314.55(c)(2)(i) because both prongs

[1] A product is considered to offer a meaningful therapeutic benefit if FDA estimates that "if approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of disease, compared to marketed products adequately labeled for that use in the relevant pediatric population" or if the drug "is in a class of drugs or for an indication for which there is a need for additional therapeutic options." 21 C.F.R. § 314.55(c)(5).

of that subparagraph must be met for you to qualify for waiver and you have not shown that your therapy, if approved, will not "represent a meaningful therapeutic benefit over existing therapies."

(3) You have met the requirement for waiver under 21 C.F.R. § 314.55(c)(2)(ii) since you have shown that necessary studies are impossible or highly impractical because the number of such patients is so small or geographically dispersed.

On the basis of this showing, under 21 C.F.R. § 314.55(c)(2)(ii) a full waiver of the requirement for pediatric studies is granted.

Under Section 505(j)(2)(C)(i) of the Act, the Agency must approve a suitability petition seeking a dosage form which differs from the dosage form of the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing dosage form.

As noted above, the Agency has waived the requirement for pediatric studies under the waiver provisions of the Pediatric Rule. Moreover, the Agency finds that the change in dosage form for the specific proposed drug products do not pose questions of safety or effectiveness in the adult population because the uses, dose, and route of administration of the proposed drug products are the same as those of the listed drug products. The Agency concludes, therefore, that investigations are not necessary in this instance and that approval of your suitability petition is therefore appropriate. If shown to meet bioavailability requirements, the proposed drug products can be expected to have the same therapeutic effects as the listed reference drug products.

The approval of this petition to allow an ANDA to be submitted for the above-referenced drug products does not mean that the Agency has determined that an ANDA will be approved for the drug products. The determination of whether an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

For your information, the listed drug products to which you refer are covered by a period of patent protection and exclusivity which appear in the Approved Drug Products With Therapeutic Equivalence Evaluations, 19th Edition, published by the Agency. The existence of such a patent protection and exclusivity will require a patent certification and an exclusivity statement upon submission of an ANDA for your proposed drug products and may also affect the approval date of any ANDA.

To permit review of your ANDA submission, you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved, the drug products will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you submit your protocol to the Office of Generic Drugs, Division of Bioequivalence for these drug products prior to the submission of your ANDA. During the review of your application, the Agency may require the submission of additional information.

The listed drug products to which you refer in your ANDA must be the ones upon which you

based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, MD 20852.

Sincerely yours,

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research